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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,424	12/28/2000	Adrian Auf Der Maur	27656/37021	7858

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MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,424	DER MAUR ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31, 33-38 and 42-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33-38 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/2006 has been entered.

Status of Claims

Claims 31, 33-38 and 42-47 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Rejections

In view of the amendments to the claims and applicants' arguments the 35 USC 112, first paragraph rejections are withdrawn.

Claim Rejections - 35 USC § 112

Claims 31, 33-38 and 42-47, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection

The following newly added claimed limitations "transcriptional activation ***domain***", "the expression of which is mediated by the interaction of the transcriptional activation ***domain*** with a DNA binding domain wherein the interaction of the transcriptional activation domain with the DNA binding domain is ***not dependent upon the presence of the antigen for which the intrabody is specific***" are not supported in the as-filed specification. The single specific transcriptional activation domain recited in the original disclosure would not provide support for the presently broad claimed domain. MPEP 714.02 specifically states that applicants should point out where in the specification the new claim limitations appear.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31, 33-38 42-47, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 31 is indefinite and unclear as to whether the step of transforming a host cell with a fusion protein also contains or is transformed with a DNA binding domain for the transcriptional activation domain and DNA binding to occur. It is also unclear from the method steps how the interaction of a domain of a transcriptional activation and DNA binding domain expresses a marker protein that identifies an intrabody to be stable and soluble. It appears that an essential step or element is lacking in the method.

2. Claim 31 is confusing and unclear as to the "selected conditions" of an intracellular intrabody, especially in the absence of positive support in the specification. The specification teaches only under reducing conditions that the intrabodies are not stable and soluble.

3. The negative limitation "..not dependent upon the presence of the antigen for which the intrabody is specific" is unclear, especially in an uncontrolled intracellular environment where antigen presence is inevitable. It is unclear from the

method how said identification is determined, absent essential step of such determination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 31, 33, 35-38 and 43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin et al(PNAS) or Hoeffler for reasons set forth in the last Office action.

Response to Arguments

Applicants acknowledge that Visintin and Hoeffler assays will give a positive signal if an intrabody is soluble, stable and specific for the target antigen. But argue that they will not give a signal (they will report a false negative) when the intrabody is soluble and stable but is not specific for the target antigen. Applicants further argue that there is no disclosure of methods for testing stability prior to testing for antigen specificity in Visitin and indeed its "model selection" system described in the text bridging pages 11726 and 11727 relied upon the use of the AMCVp41/BTN116 bait with the scFVF8-VP16 fusion protein wherein the scfv portion is an anti-ACMV antibody.

In response, it is sufficient that Visintin discloses that the intrabody is soluble and stable under the selected intracellular conditions albeit interaction with the antigen is made. As applicants state a false negative signal is obtained in the absence of antigen. Simply because Visintin is silent in the assay of scFv's stability and solubility in the absence of antigen does not mean that one would not able to determine such assay. The claims recite an open-ended language "comprising" even with presently added negative limitation "not dependent upon the presence of the antigen for which the intrabody is specific". The Visintin assay determines simultaneously the stability (using the two-hybrid system, as applicants did) and antigen of the intrabody. Such assay would render obvious the two separate methods of applicants i.e., determining first stability and then antigen reaction of the intrabody. It is not apparent how the two-hybrid system employed by Visintin, as employed by applicants, would produce a different results. Like applicants, Visintin is solving the same problem of stability and solubility of the antibody under intracellular conditions. [It is of interest to note at page 11723, col. 1 and col. 2, the Visintin's comment regarding the solubility and stability of intrabodies. Visintin states that when antibodies are expressed in the cell cytoplasm, folding and stability problems often

occur resulting in low expression levels and limited half-life of antibody domains. These problems mostly are caused by the reducing environment of the cell cytoplasm, which hinders the formation of the intrachain disulfide bond of the VH and VL domains and is important for the stability of the folded proteins.] Visintin recognizes that there is a need to obtain antibody fragments that will fold and are stable and soluble under conditions of intracellular expression. The two-hybrid system (which is the same as used in the instant disclosure) is used to monitor intracellular antigen-antibody interactions via reporter gene activation. The use of reporter assays to detect antibody-antigen interaction in vivo thus provides a strategy to select those individual antigen-specific scFv that can function in cells. Visintin at page 11726 states that the use of the two-hybrid assay for intracellular antigen-antibody interactions should allow the isolation of antibody domains that tolerate the absent of the intra-chain disulfide bond in the reducing environment of the cytoplasm. Many of these intracellular do not function inside cells. At page 11727, col. 2 Visintin states that the paucity of functional intracellular scFv requires selection procedures that are based on intracellular action rather than in vitro antigen binding alone. The two-hybrid assay is a general assay that depends upon that the interaction of

scFv with antigen under intracellular conditions. Because under intracellular conditions the antibody is unstable and not soluble. The folding stability of antibody domains are contributed by many residues in the frameworks with different scFv fragments having different overall stabilities. Good intracellular expression is related to additional parameters such as solubility versus propensity to aggregate, cellular half-life and others. (Note that neither Exhibit A nor B is shown in the as-filed specification and for the reasons above does not overcome the rejection.)

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable Visintin above in view of Ptashne et al (20040014036) for reasons of record.

Response to Arguments

Applicants argue that Ptashne is directed to use of a two-hybrid system using Gal4 and Gal11p but does not teach the basic invention of claim 36 from which claim 42 depends.

In response, the instant disclosure teaches also a two-hybrid system as claimed. Applicants cannot attack the references individually when the rejection is based on the combination of references. Thus, while Ptashne does not teach the basic invention of claim 36, Visintin does. The combined teachings of the disclosure would therefore lead one having

ordinary skill in the art at the time the invention was made to the claimed method.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin as applied to claims 31, 33, 35-38 and 43-47 above, and further in view of Martineau (J. Mol.Biol.) or Nolan et al (USP 6,153,380) for reasons of record.

Response to Arguments

Applicants argue that Martineau and Nolan are directed to marker proteins but do not teach the invention of claim 31 from which claim 34 depends.

In reply, the response above over Ptashne is applied herein since applicants present nearly the same arguments, except drawn to the argued marker taught by each of Martineau and Nolan.

Double Patenting

Claims 31, 33-38, 43-47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23 and 39 of copending Application No. 10/169,179('179 application) for reasons of record.

Response to Arguments

Applicants urge deferring this rejection until an indication of allowable claims in both applications are made. At

that time applicants will consider the allowable claims of each case and either submit arguments that the claims are unobvious over each other or submit a terminal disclaimer.

In response, in the absence of a terminal disclaimer, the rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
October 14, 2006